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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: BAUMANN et al.

Title: OLIGONUCLEOTIDES AND METHODS FOR DETECTING HEPATITIS C VIRAL NUCLEIC ACIDS

Appl. No.: 10/011,855

Filing Date: December 4, 2001

Examiner: Bao Qun Li

Art Unit: 1648

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the United States Patent and Trademark Office, Alexandria, Virginia on the date below.

Germaine Sarda
(Printed Name)

(Signature)

November 4, 2004
(Date of Deposit)

DECLARATION OF MICHAEL LEWINSKI, PH.D UNDER 37 C.F.R §1.132

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Michael Lewinski, Ph.D. hereby declare as follows:

1. I was educated in the biomedical sciences at California Lutheran University where I received a B.S. degree and I received a M.S. degree from California State University, Northridge. I attended University of California, Los Angeles in the School of Medicine where I received a Ph.D degree in Microbiology and Immunology.

2. I was a postdoctoral fellow in Clinical and Public Health Microbiology at UCLA. For the 12 years, I have held various scientific positions at MRL Reference Laboratory (Focus Technologies, Inc) and Quest Diagnostics. I have been a laboratory director at Quest Diagnostics Nichols Institute since October of 1997.

3. In total, I have worked more than 12 years in the field of nucleic acid diagnostic assays for infectious diseases. I am the author or co-author of over 30 published scientific articles and abstracts in this field. A brief summary of my accomplishments and a recent copy of my Curriculum Vitae is attached as APPENDIX 1.

4. I am an inventor of the above identified patent application. I understand that the Examiner has rejected the claims as being obvious over a combination of prior art references. According to the Examiner, it would be obvious to take various features from these references and combine them to obtain the claimed invention and that there would have been a reasonable expectation of success in achieving the combination. The Examiner bases this conclusion on the belief that because the entire sequence of HCV is known, it would require nothing more than ordinary skill to develop an HCV assay using any particular primer or probe sequence that can be derived from the HCV genome. In my opinion, this rationale is flawed. My own experience from 12 years of assay development and from others who have published in this field leads me to conclude that the quality of a nucleic acid based assay is very much dependent on the particular primers and probe sequences chosen and that there is no way to know in advance that any particular sequences would be effective.

5. Exemplary of my experience is a publication by Wang et al., *BioTechniques* 17: 82-87 (1994) (already of record), which teaches the importance of particular primer pairs in the sensitivity of detecting target nucleic acids in PCR. Wang et al. teaches that primers that differ even "slightly" in position can exhibit 100- to 1000-fold differences in amplification sensitivity. Wang et al. describes dramatic differences in sensitivity using different primer combinations. As stated by Wang et al.:

> Our results suggest that primers are decisive for the sensitivity of PCR, and that there is no reliable means to predict the sensitivity achieved by a given primer pair. Some primer pairs, which have been designed taking into account the basic rules, do not work as efficiently as expected. An extensive search for optimal reaction protocol may be unfruitful with these primers.

Wang et al., page 85, paragraph 5 (emphasis added in bold). I am familiar with this uncertainly in prior pair selection reported by Wang et al. as are others in my field. In addition, I have not found any reliable means to predict with reasonable certainty which primer pairs can be successfully employed in the detection of a given target nucleic acid.

6. Furthermore, it is my experience that TaqMan assays are more complex than standard PCR assays because the primers and the probe in a TaqMan format must be able to

extended from the primers. The probe in standard PCR is applied after the PCR has been completed and amplicons generated. Because of the more stringent working requirements, primers pairs and probes that might work acceptably in standard PCR are more likely to fail or perform poorly in the TaqMan format. I conclude from this that there would not have been a reasonable expectation of success for combining the probes of Resnick et al. and the probe of Michinori et al., both from standard PCR assays, for use in a TaqMan style PCR assay such as described in Kleiber et al. as asserted by the Examiner.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the captioned patent application or any patent issued therefrom.

November 1, 2004
Date

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Michael A. Lewinski, Ph.D., D(ABMM)

Date of Birth March 4, 1957

Place of Birth Detroit, Michigan

Citizenship United States of America

Personal Married, three children

Education

1990 - 1992 UCLA Medical Center Los Angeles, CA
Postdoctoral Fellow
- American Academy of Microbiology: Continuing Postdoctoral Education Program in Medical and Public Health Laboratory Microbiology.
- Clinical rotations: UCLA Medical Center, West Los Angeles Veterans Administration Hospital and Los Angeles County Public Health Laboratories.

1986 - 1990 UCLA School of Medicine Los Angeles, CA
Doctor of Philosophy, Microbiology and Immunology

1980 - 1985 California State University, Northridge Northridge, CA
Master of Science, Biology (Major: Microbiology)

1975 - 1979 California Lutheran University Thousand Oaks, CA
Bachelor of Science, Biology

Licenses and Certificates

Diplomate, American Board of Medical Microbiology, July 1, 2001 (922)

Clinical Microbiologist Scientist, California (MTE670)

Clinical Laboratory Specialist, Molecular Biology (NCA)

Certificate of Qualification: Laboratory Director of Bacteriology, Diagnostic Immunology, Mycobacteriology, Mycology, Parasitology, and Virology, New York State Department of Health.

Professional Experience

1997 - Present Quest Diagnostics, Inc. San Juan Capistrano, CA

Scientific Director, Infectious Diseases

- Responsible for the clinical microbiology, virology, molecular microbiology, and serology services in a reference laboratory specializing in esoteric tests.
- Responsible for the research, development, and validation of new procedures and tests.
- Assistant Medical Director of Record, Infectious Diseases
- Member, Infectious Disease Sub-Specialty Committee
- Member, Genomics Innovation Team
- Chair, Molecular Diagnostics Best Practices Team

1992 - 1997 MRL Reference Laboratory Cypress, CA

Associate Director, Microbiology, Virology, and Molecular Diagnostics

- Responsible for the clinical microbiology, virology, and molecular diagnostic services in a reference laboratory specializing in esoteric tests.
- Responsible for the research, development, and validation of new procedures and tests.
- Reported to the General Manager and Scientific Director

1995 - 1997 Health Line Clinical Laboratory Burbank, CA

Consultant, Microbiology

- Establish and implement protocols for routine bacteriology in a laboratory servicing doctor's offices.
- Provide consultation services on difficult cases.
- Perform routine bacteriology as needed (e.g., staff shortages, vacation coverage).

1997 Bausley & Associates Anaheim Hills, CA

Consultant, Microbiology

- Consultant for an engineering firm hired by insurance companies to evaluate claims involving a potential microbiologic etiology (e.g., sick building syndrome, food poisoning, etc.).
- Performed visual inspections of structures, collected environmental samples and performed quantitative microbiology in suspected cases of sick building syndrome.
- Performed microbiology services as required in other case scenarios (e.g., food poisoning cases).
- Evaluated data and prepared written reports detailing findings and recommendations.

1986 - 1992 Los Robles Hospital Thousand Oaks, CA

Clinical Laboratory Technician

- Laboratory assistant on the night shift in a 220 bed hospital and trauma center.
- Performed phlebotomy in the emergency room, intensive care, neonatal intensive care and coronary care wards.
- Processed specimens and ran tests.
- Set-up microbiology cultures
- Performed nightly computer operations and quality control.

1983 - 1986 California Amplifier, Inc. Camarillo, CA

Manufacturing Manager

- Director of Manufacturing, Commercial Products Division, of a high-tech electronics firm manufacturing microwave products for both the military and private sectors.
- Chair, Manufacturing and Safety Committees
- Member, Change Control, Design Review, and Material Review Boards.
- Responsible for two departmental managers (production and test), six supervisors, and approximately 150 employees.
- Other positions held include Program Manager, Production Manager, and Production Supervisor.
- Developed working knowledge of Critical Path Management and Program Evaluation Review Technique.
- Reported to the Vice President, Operations

1982 - 1983 Veterans Administration Hospital Sepulveda, CA

Research Assistant

- Gallbladder diseases research, using an animal model, for the investigation of the mechanisms of cholesterol gallstone formation following vagotomy, ileal resection and/or long term TPN exposure.
- Performed minor surgeries and assisted with major surgical procedures.
- Performed all fluorescent and electron microscopy.
- Studies performed in conjunction with the Department of Surgical Research, UCLA School of Medicine.

Teaching Experience

1987, 1988 UCLA School of Medicine Los Angeles, CA

Teaching Assistant

- Responsible for teaching laboratory sections in Medical Bacteriology to second year medical students.

1985, 1987 California Lutheran University Thousand Oaks, CA

Part-time Faculty, Medical Microbiology

- Responsible for teaching both lecture and laboratory sections of an upper division course in Medical Microbiology (Biology 473).

1980 - 1983 California State University, Northridge Northridge, CA

Teaching Assistant

- Taught laboratory sections in Introductory Microbiology, Human Anatomy and Medical Microbiology.

Professional Memberships

American Society for Microbiology

Southern California - American Society for Microbiology, President, 2001–Present, (President Elect, 1999 – 2001)

Member, NCCLS Subcommittee on Genotyping for Infectious Disease: Identification and Characterization, October 2001 to Present.

Honors and Awards

Associate Member, Sigma Xi, National Scientific Research Honor Society (1984).

Winner, Graduate Colloquium, Southern California - American Society for Microbiology (1983).

Research Grant, Students Projects Committee, California State University Foundation, Northridge (1982).

Community Activities

Coaching youth flag and tackle football

Interests and Hobbies

Sports, reading, music, and the outdoors (camping and fishing)

Abstracts

1. Baumann, R.E. and M.A. Lewinski. Performance evaluation of a semi-automated HIV-1 RNA assay using QIAGEN BioRobot RNA isolation and AMPLICOR HIV-1 MONITOR, version 1.5 detection. 102nd General Meeting, American Society for Microbiology, Salt Lake City, Utah. May 19 – 23, 2002. C-214.

2. Exner, M.M. and M.A. Lewinski. Isolation and detection of Herpes Simplex Virus in respiratory specimens from patients using the Roche MagNA Pure and LightCycler instruments. 102nd General Meeting, American Society for Microbiology, Salt Lake City, Utah. May 19 – 23, 2002. C-231.

3. Baumann, R.E., H. Hamdan, and M.A. Lewinski. Evaluation of a COBAS TaqMan Hepatitis C quantitative assay. Clinical Virology Symposium (18th), Clearwater Beach, Florida. April 28 – May 1, 2001. S17.

4. Duong, D., A. McCarthy, R. Prieur, M.J. Rosenstraus, W. Robinson, B. Boyer, and M.A. Lewinski. Automation of the Roche CT/NG PCR assay for the qualitative detection of Chlamydia trachomatis and Neisseria gonorrhoeae from clinical specimens: a potential solution for high volume nucleic acid amplification testing. 101st General Meeting, American Society for Microbiology, Orlando, Florida. May 20 – 24, 2001. C-197.

5. Harrington, E.R., R. Nabi, and M.A. Lewinski. Direct identification of Mycobacterium spp. from smear positive concentrates by HPLC profiles and INSTEP software. 101st General Meeting, American Society for Microbiology, Orlando, Florida. May 20 – 24, 2001. C-365.

6. Baumann, R.E. and M.A. Lewinski. Evaluation of semi-automated Hepatitis C RNA quantitative assays using Qiagen biorobot RNA isolation and COBAS AMPLICOR HCV MONITOR detection. 15th Annual Meeting of AACC, San Diego, California. November 2000. 25.

7. Harrington, E.R., L. Messier, and M.A. Lewinski. Performance characteristics of the BDProbeTec™ ET System for detection of Chlamydia trachomatis and Neisseria gonorrhoeae. American Society for Microbiology, 100th General Meeting, Los Angeles, California, May 21-25, 2000. C-374.

8. Harrington, E., W. Meyer, L. Wardzala, and M. Lewinski. Effect of temperature variation during shipment and storage on the stability of HIV RNA in plasma collected in BECTON-DICKINSON VACUTAINER® PPT™ tubes. ICAAC (39th), Toronto, Canada, September 26 - 29, 1999. 1580.

9. Popov, J., S. Tom, M. Lewinski, and A. Sferruzza. Evaluation of PREMIER PLATINUM HpSA assay for the detection of *Helicobacter pylori* in stool specimens. 99th General Meeting, American Society for Microbiology, Chicago, Illinois, May 30 - June 3, 1999.

10. Hamdan H., M. Cohen, B. Green, J. LeBault, D. Duong, R. Kagan, R. Fenwick, and M. Lewinski. Typability of HIV-1 specimens received for HIV-1 genotyping for drug resistance in a clinical reference laboratory. 13th Annual San Diego Conference in San Diego, California, November 19-21, 1998.

11. Hamdan H., D. Duong, R. Kagan, M. Fortich, R. Khuu, S. Zhu, R. Fenwick, and M. Lewinski. Frequency of Hepatitis C Virus genotypes as determined by direct sequencing of the NS5b region in a clinical reference laboratory. 13th Annual San Diego Conference in San Diego, California, November 19-21, 1998.

12. Lewinski, M., C.A. Miller, B. Kasten, and D. Armstrong. National survey of grepafloxacin against community isolates of common respiratory pathogens. 36th Annual Meeting of the Infectious Diseases Society of America, Denver, Colorado, November 12-15, 1998.

13. Lewinski M., C.A. Miller, B. Kasten, and D. Armstrong. Activity of grepafloxacin against community isolates of penicillin-resistant *Streptococcus pneumoniae.* International Symposium on New Quinolones, Denver, Colorado, November 15-17, 1998.

14. Lewinski, M.A., S.K. Bruce, S.W. Peres, K.A. Devor and R.K. Porschen. HPLC identification of mycobacterial species isolated from the MB/BacT® detection system. American Society for Microbiology, 98th General Meeting, Atlanta, May 17-21, 1998.

15. Meyer W.A., S. Tom, L. Verano, Y. Lue, and M. Lewinski. Stability of Herpes Simplex Virus in clinical specimens: Comparison of virus recovery from "fresh" and "overnight-shipped" samples. PACSV Meeting, Clearwater, Florida, April 1998.

16. Lewinski, M.A., S.M. Mendoza, D.A. Bruckner, and D.R. Scholl. An evaluation of the ELVIS HSV test system modified to detect, identify, and type HSV isolates from clinical specimens. ICAAC (37th), Toronto, Canada, September 28 - October 1, 1997. H-96

17. Lewinski, M.A., S.M. Mendoza, and R.K. Porschen. Comparison of four immunofluorescent assays in a retrospective study for the detection of Cytomegalovirus by shell vial methodology. Clinical Virology Symposium, Clearwater, Florida, April 28 - May 1, 1996. S9.

18. Thomas, J.A., R.G. Wright, M.A. Lewinski, and M.G. Golightly. Simultaneous detection of IgG and IgM antibodies to *Treponema pallidum* and *Borrelia burgdorferi* antigens using a flow microsphere immunoassay (FMIA). V International Conference on Lyme Borreliosis, Arlington, Virginia, May 30 - June 2, 1992. 85.

19. Hindler, J.A., M.A. Lewinski, and D.A. Bruckner. Rapid antimicrobial susceptibility testing of Gram negative bacilli using the MicroScan®-W/A and Vitek automated systems. Abstracts of the Annual Meeting of the American Society for Microbiology. C214.

20. Hindler, J.A., M.A. Lewinski, and D.A. Bruckner. Rapid automated susceptibility testing of *Enterococcus* spp. and *Staphylococcus* spp. Abstracts of the 30th ICAAC. 1074.

21. Lewinski, M.A. and N.H. Bishop. Demonstration of the binding of specific polyclonal immunoglobulin G to *Treponema pallidum*, Nichols strain, by electron microscopy. Abstracts of the Annual Meeting of the American Society for Microbiology. 1984. 70.

Publications

1. Blanco, D.R., C.I. Champion, M.A. Lewinski, E.S. Shang, S.G. Simkins, J.N. Miller, and M.A. Lovett. 1999. Immunization with *Treponema pallidum* outer membrane vesicles induces high-titer complement-dependent treponemicidal activity and aggregation of *T. pallidum* rare outer membrane proteins (TROMPs). J Immunol 163(5): 2741-6.

2. Lewinski, M.A., J.N. Miller, M.A. Lovett, and D.R. Blanco. 1999. Correlation of immunity in experimental syphilis with serum-mediated aggregation of *Treponema pallidum* rare outer membrane proteins. Infect Immun. 67(7): 3631-6.

3. Lewinski, M.A., J.N. Miller, C.I. Champion, E.M. Walker, L.A. Borenstein, R.J. Gayek, M.A. Lovett, and D.R. Blanco. 1995. Treponemicidal antibody measured by the "washed-killing" assay correlates with immunity in experimental rabbit syphilis. Sexually Transmitted Diseases 22 (1):31-38.

4. Blanco, D.R., E.M. Walker, C.I. Champion, M.A. Lewinski, M.A. Lovett, G.A. Zampighi, D.A. Haake, L.A. Borenstein, and J.N. Miller. 1990. Cellular and molecular pathogenesis of syphilis. Ayoub, E.M., G.H. Cassell, W.C. Branche, Jr., and T.J. Henry (eds.) *In* Microbial determinants of virulence and host response. © American Society for Microbiology, Washington DC Chapter 15.

5. Muller, E.L., M.A. Lewinski, and H.A. Pitt. 1985. Action of cholecystokinin on sphincter of oddi phasic wave activity in the prairie dog. Current Surgery 42:128-130.

6. Muller, E.L., M.A. Lewinski, and H.A. Pitt. 1984. The cholecysto-sphincter of oddi reflex. Journal of Surgical Research 36:377-383.

7. Pitt, H.A., M.A. Lewinski, E.L. Muller, V. Porter-Fink, and L. Den Besten. 1984. Ileal resection-induced gallstones: altered bilirubin or cholesterol metabolism. Surgery 96:154-160.

In Preparation

1. Exner, M.M. and M.A. Lewinski. 2002. Sensitivity of multiplex real-time PCR reactions, using the LightCycler and the ABI PRISM 7700 sequence detection system, is dependent on the concentration of the DNA polymerase. Molecular and Cellular Probes. In press.

Invited Lectures

1. Lewinski, M.A. Quantitation of Cytomegalovirus: methodologic aspects and clinical applications. ChromaVision Medical Systems Inc., San Juan Capistrano, California, January 7, 1999.

2. Lewinski, M.A. Laboratory testing for HIV. Northwest Florida Laboratory Association 1998 Convention, Pensacola, Florida, May 7, 1998.

3. Lewinski, M.A. New and emerging rapid technologies in mycobacteriology. *In* Update in clinical diagnosis of infectious diseases. Medical Symposium hosted by the Cantacuzino Institute in Bucharest, Romania, April 20-24, 1998.

4. Lewinski, M.A. New and emerging rapid technologies in mycobacteriology.

   - CLMA, Inland Empire, Blood Bank of Riverside and San Bernardino Counties, May 27, 1998.
   - California State Clinical Laboratory Scientists, Inland Empire Chapter, University of California, Riverside, March 7,1998
   - California State Clinical Laboratory Scientists, Riverside, California, January 1, 1998.
   - CAMLT Seminar Series, San Luis Obispo, CA, March 16, 1996.
   - California Society for Clinical Laboratory Science, Burbank, California, February 24, 1996.
   - California State Clinical Laboratory Scientists, Annual Meeting and Convention, Red Lion Inn, Ontario, CA. May 3, 1996.
   - Continuing Education Lecture Series, Westlake Medical Center, Westlake Village, CA. December 19, 1994.
   - CAMLT Spring Seminar. *In* Current topics in mycobacteriology. Berlin, G. and M.A. Lewinski. Santa Barbara, CA. April 16, 1994.

5. Lewinski, M.A. (moderator). Clinical microbiology in the next millennium. *In* A new age for microbiology. Southern California Branch of the American Society for Microbiology, Irvine, California, November 6-8, 1997.

6. Lewinski, M.A. 1995. Enteroviruses: diseases and laboratory diagnosis. In Today's virology challenges: respiratory viruses, enteroviruses, and CMV. Virology Workshop. Presented in cooperation with Chemicon International, Inc., The Turnip Rose Banquet and Conference Center, December 7, 1995.

7. Lewinski, M.A. 1995. The virology laboratory and the diagnosis of disease. *In* Laboratory diagnosis of viral infections. 12th Annual Northwest Medical Laboratory Symposium. Portland, Oregon, Session No. 19, October 19, 1995.

8. Lewinski, M.A. 1995. Legionella and mycoplasma infections and the laboratory diagnosis of disease. Continuing Education Program, St. Vincent Medical Center Clinical Laboratories. August 2, 1995.

9. Lewinski, M.A. 1994. Clinical application of DNA probes. California Association of Bioanalysts Convention, Lake Tahoe, April 7 - April 10, 1994.

10. Lewinski, M.A. 1993. Syphilis: shedding new light on an age old disease. Department of Biology, Microbiology Seminar Series, California State University, Long Beach, October 20, 1993.

11. Lewinski, M.A., Berlin, G., C. Gagne, and E. Desmond. 1993. Mycobacteriology Workshop. California State University, Los Angeles. Hardy Diagnostics (sponsor). June 5, 1993.

12. Lewinski, M.A. 1993. The polymerase chain reaction. Los Robles Regional Medical Center, Continuing Medical Education Lecture Series.

13. Lewinski, M.A. 1992. Practical strategies for the laboratory diagnosis of syphilis and Lyme borreliosis. ASM Audioconference Series, January 28, 1992.

References Available upon request.